REMARKS

I. Preliminary Remarks

The application as filed included claims 1-30. Claims 1-30 were subsequently canceled and new claims 31-66 were added. In response to the restriction requirement imposed by the Office, Group I (claims 31-46 and 48-50) were elected for continued examination. Claims 47 and 51-66 were withdrawn by the examiner. The examiner acknowledged applicants' request for rejoinder of the withdrawn process claims 57-66 after allowable subject matter has been indicated.

Applicants respectfully request acknowledgement from the examiner that the proper procedure under MPEP § 809.02(a) will be followed for claims 51-56. The cited section of the MPEP states that "***Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim*** as provided by 37 CFR 1.141 [emphasis added]" Thus, upon allowance of a generic claim (such as claim 31), applicants will be entitled to consideration of claims 51-56, directed to additional species, if such claims depend from the allowed generic claim.

II. Explanation of Amendments to the Specification

The specification has been amended to capitalize the trademarks mentioned throughout the application as suggested by the examiner. No new matter has been amended by the amendments to the specification.

III. The Objection to the Claims May Properly Be Withdrawn.

The examiner objected to claims 38-40, directed to antibody fragments, as being of improper dependent form for failing to further limit the subject matter of a previous claim (claim 33). Applicants respectfully disagree and request reconsideration in view of the following.

The specification at page 6, lines 28-30 defines the term "antibody" to include "polyclonal or monoclonal antibodies, humanized or chimeric antibodies and ***antibody fragments*** such as single chain Fv antibody fragments, Fab fragments, and $F(ab)_2$ fragments. [emphasis added]" Claim 33 recites "wherein the non-Aβ polypeptide is an antibody." When read in light of the definition of the term "antibody" in the specification, claim 33 clearly encompasses antibody fragments such as the fragments specifically recited in claims 38-40. Therefore, claims 38-40

properly define and further limit the subject matter of claim 33, and the objection may properly be withdrawn.

IV. The Rejection Under 35 U.S.C. § 112, Second Paragraph, May Properly Be Withdrawn.

The examiner rejected claims 35 and 41-46 under 35 U.S.C., § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the examiner alleges that claim 35 is vague and indefinite for recitation of an antibody with "specific binding affinity for amyloid comprising residues 1-39 of SEQ ID NO: 1" because it is not clear if the specific binding is limited to binding to a specific epitope, or to a protein from a particular species, or both.

Applicants note that the reference to residues 1-39 of SEQ ID NO: 1 is not meant to refer to an epitope but is simply meant to provide an amino acid sequence to identify "amyloid" protein and distinguish amyloid protein from other unrelated proteins. Applicants respectfully submit that one of ordinary skill in the art would understand what is meant by the term "specific binding affinity to amyloid" as that term is used in the claim and in view of its usage in the specification and the art.

For example, Harlow et al., states "The usefulness of monoclonal antibodies stems from three characteristics—their specificity in binding, their homogeneity, and their ability to be produced in unlimited quantities. The production of monoclonal antibodies allows the isolation of reagents with a unique, chosen specificity." Harlow et al. (Eds), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor , NY (1988), Chapter 6. Thus, one of ordinary skill in the art would understand the term "specific binding affinity" to indicate that the antibody of the invention recognizes and preferentially binds amyloid with no substantial cross-reactivity (i.e., able to distinguish amyloid from other polypeptides), but may also interact with other proteins (for example, in the case of an antibody which can also bind *S. aureus* protein A or other antibodies in ELISA techniques). See Harlow et al. Chapters 6 and 11.

This art recognized usage of this term is confirmed by page 6, lines 22-77 of the specification, which specifically references U.S. Pat. No. 5,262,332 for examples of antibodies having specific binding affinity for Aβ. U.S. Pat. No. 5,262,332 teaches that antibodies "specific" for amyloid are able to distinguish amyloid protein from other proteins and gives an example of a competition assay that can be carried out to confirm the specificity of antibodies to β-AP. When the

is reduced when they are pre-incubated with purified amyloid before application to the tissue samples. See assay described at Col. 9, lines 5-31 of U.S. Pat. No. 5,262,332:

> To confirm the specificity of antibodies to β-AP, they were absorbed with highly purified β-AP. While the β-AP-specific antibodies detected the tissue deposits before this absorption, they did not do so afterwards, confirming that they were in fact detecting β-AP as deposited in the skin or intestine. Similarly, the antibodies stained β-amyloid deposits in the brain before, but not after, the antibodies were absorbed with β-AP specific antigen. Antigen-absorbed and "control-absorbed" aliquots (both in 150 mM NaCl, 50 mM Tris, pH 7.6) were reacted simultaneously with AD brain sections, AD skin or intestine sections and dot blots of the β-AP-containing antigen. In the case of antiserum A, for example, a partially purified fraction of detergent-extracted senile plaque cores from AD cerebral cortex (as described in Example IA, below) was used as the absorbent; a "control absorption" employed a fraction prepared identically from normal aged human cerebral cortex which contained the contaminating particles of core fractions (e.g., lipofuscin granules, collagen, and microvessel fragments). In each such experiment, the AD plaque core absorption markedly diminished or abolished the staining of plaque and vascular amyloid in AD brain, the dermal and subdermal amorphous β-AP deposits, and the β-AP-containing antigen on dot blots. The control absorptions produced no change in these immunoreactions.

Thus, one of ordinary skill, in light of common knowledge in the art and the usage of the term in the specification would understand that the term "specific binding affinity" in claim 35 means that the antibody distinguishes amyloid from other proteins and binds to an epitope within residues 1-39 of SEQ ID NO: 1.

V. The Rejection Under 35 U.S.C. § 102(b) May Properly Be Withdrawn.

The examiner rejected claims 31-34, 42 and 43 under 35 U.S.C. § 102(b) as allegedly being anticipated by Saito et al., Proc. Natl. Acad. USA, 92:10227-10231, 1995 (hereinafter "Saito"). The examiner states that "claims 31-34, 42 and 43 are directed to a composition comprising an Aβ polypeptide of residues 1-39 of SEQ ID NO: 1 linked to a non-Aβ polypeptide. Document of Saito et al. discloses composition comprising an $A\beta^{1-40}$ polypeptide linked to a monoclonal antibody in a pharmaceutically acceptable solution." Applicants respectfully traverse the rejection and request reconsideration in light of the above amendments and the following remarks.

In response, applicants have amended claim 31 to recite, in part, that the "non-Aβ polypeptide" is "a diagnostic or therapeutic agent for a disorder of the central nervous system (CNS)."

Support for this amendment is found, e.g., at page 6, lines 8-9 of the specification. Anticipation requires that the cited art disclose each and every element of the claims, which is not the case here.

Saito discloses a composition comprising a vector-mediated drug delivery system composed of a conjugate of $A\beta^{1-40}$, streptavidin, biotin and the OX26 monoclonal antibody to the transferrin receptor. See page 10227, 2nd column, lines 2-5 and Figure 1. None of the streptavidin, biotin, or the OX26 antibody is a diagnostic or therapeutic agent for a CNS disorder. Thus, Saito does not disclose each and every element of the claims and the rejection of the current claims under 35 U.S.C. §102(b) may properly be withdrawn.

Moreover, Saito cannot provide the basis for an anticipation rejection for new claims 67-68 because Saito does not teach or suggest that the Aβ polypeptide is covalently linked to a non-Aβ polypeptide.

VI. The Rejection of Claim 44 Under 35 U.S.C. § 103(a) May Properly Be Withdrawn.

The examiner rejected claim 44 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Saito. The examiner asserts that "it would have been *prima facie* obvious to a person of ordinary skill in the art to use Aβ 1-42 polypeptide to construct the molecule as disclosed by Saito." The examiner further asserts that "one of ordinary skill in the art would have been motivated to do so because Saito explained the construct and delivery of Aβ 1-40 molecule to the brain..." Applicants respectfully disagree with the examiner's assertions and request reconsideration in view of the following remarks.

Contrary to the Examiner's suggestion, Saito does ***not*** teach that the Aβ polypeptide enhances transport across the blood brain barrier (BBB). Instead, Saito reports a mechanism to enhance delivery across the BBB that involves the use of a vector-mediated drug delivery system involving the use of ***monoclonal antibodies to either the transferrin or insulin receptors*** to enhance transport across the BBB. See, for example, the legend to Fig. 1 on page 10228 of Saito. Therefore, in Saito's vector delivery system, the monoclonal antibody, and ***not*** Aβ, enhances transport across the BBB through receptor-mediated transport of the monoclonal antibody.

The present invention, however, reports that the Aβ polypeptide itself is the transport vehicle for the non-Aβ polypeptide and further contains data indicating that the BBB permeability of a

composition containing Aβ bound to a monoclonal antibody (e.g., nonspecific antibody or antibody specific for $A\beta^{1-42}$) was significantly greater than that of the monoclonal antibody alone.

Moreover, one of ordinary skill in the art would not have been motivated to arrive at the claimed invention based on Saito because doing so would go ***against the express teachings*** of Saito. Saito does not teach or suggest that the Aβ polypeptide itself is capable of enhancing transport of a non-Aβ polypeptide across the BBB. Rather, Saito teaches that "...unconjugated $A\beta^{1-40}$ undergoes negligible transport through the BBB *in vivo*..." (page 10230, 1st column). Therefore, upon review of Saito, one of skill in the art would be led to avoid using Aβ as a transport vehicle to cross the BBB and correspondingly would not be motivated to conjugate Aβ to a diagnostic or therapeutic agent for CNS disorders. Furthermore, because Saito reports that unconjugated Aβ undergoes negligible transport across the BBB, one of skill in the art would find no reasonable expectation of success in Saito to arrive at the claimed invention.

Therefore, in view of Saito's teaching away from the claimed invention and the lack of reasonable expectation of success, Applicants respectfully submit that the claims are novel and inventive over Saito, and reconsideration and withdrawal of the rejection is respectfully requested.

VII. The Rejection of Claims 36-40 and 49-50 Under 35 U.S.C. § 103(a) May Properly Be Withdrawn.

The examiner rejected claims 36-40 and 49-50 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Saito in view of Solomon et al., (WO 99/60024). The examiner asserts that "it would have been obvious to a person of ordinary skill in the art to modify chimeric polypeptide of Saito to include fragments or chimeric antibodies in the construct, or to label the antibody." Applicants respectfully disagree with the examiner's assertion and request reconsideration in view of the following remarks.

As discussed above in Section VI, Saito does not teach or suggest the claimed composition, and therefore cannot provide the basis for an obviousness rejection for any of the pending claims. Solomon, which teaches the well-known art of labeling antibodies for diagnostic and research purposes, fails to provide the disclosure lacking from Saito. Accordingly, applicants respectfully submit that claims 36-40 and 49-50 and novel and inventive over Saito in view of Solomon and the rejection may properly be withdrawn.

VIII. The Rejection of Claims 41 Under 35 U.S.C. § 103(a) May Properly Be Withdrawn.

The examiner rejected claim 41 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Saito in view of Poduslo (U.S. Patent No. 5,670,477). The examiner asserts that "it would have been obvious to a person of ordinary skill in the art to conjugate a molecule intended for delivery through blood-brain-barrier to a polyamine as disclosed in '477 patent. One of ordinary skill in the art would have been motivated to do so because '477 patent specifically teaches the advantages of linking polyamine to a compound to be delivered to the brain." Applicants respectfully disagree with the examiner's assertion and request reconsideration in view of the following remarks.

As discussed above in Section VI, Saito does not teach or suggest the claimed composition and therefore cannot provide the basis for an obviousness rejection for any of the pending claims. Poduslo, which teaches modification of a compound by conjugating it to a polyamine, fails to provide the disclosure lacking from Saito. Accordingly, applicants respectfully submit that claim 41 is novel and inventive over Saito in view of Poduslo and the rejection may properly be withdrawn.

IX. Conclusion

It is believed that the foregoing responds to all of the examiner's concerns, however, if the examiner has any further questions, she is invited to contact the undersigned agent or Li-Hsien Rin-Laures, attorney for applicants, at the number below.

Dated: July 26, 2006

Respectfully submitted,

By Jeanne M. Brashear

Jeanne M. Brashear
Registration No.: 56,301
MARSHALL, GERSTEIN & BORUN
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Agent for Applicant